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DETECTION OF RETINAL ISCHEMIA PRIOR TO BLACKOUT BY ELECTRICAL EVOKED CORTICAL RESPONSES

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Loss of function in the peripheral retina due to ischemia has been successfully monitored by retinal ganglion cell responses to external electrical stimulation of the eye which evokes cortical responses detectable by scalp electrodes. The retinal ischemia has been produced by increased intraocular pressure. Cessation of both the retinal ganglion cell impulses and cortical evoked potentials is observed when the retinal blood flow is halted, although the choroidal blood flow is continued as shown by persistence of the electroretinogram (ERG) a-wave and the disappearance of all other ERG components.

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INTRODUCTION

The objective of this program was to detect as early as possible any disturbances in cortical blood flow that will lead to blackout and unconsciousness. The specific sign that has been used is occurrence of retinal ischemia which is detected by monitoring cortical responses. External electrical stimulation of the eye has been used to evoke responses from the peripheral retina while keeping disturbances of normal visual function to a minimum. The purpose of the present work is to advance our knowledge of techniques to furnish early warning of loss of brain function or blackout resulting from high positive G forces or other types of maneuvers that produce circulatory stasis in the head, particularly in the brain or eye. During the present period, background information was acquired to use for the design of such operational techniques and to compare our proposed electrical stimulation techniques with those using visual stimulation. The investigation was carried out on cats to determine if a decrease in peripheral blood flow would be equated with loss of responsiveness to electrical stimulation of peripheral portions of the retina from external electrodes. The electrically evoked cortical responses (EER or EECR) were monitored by scalp electrodes in the region of the inion in a manner similar to the responses evoked by visual stimulation (VER). The data gathered during this program suggests that the EER approach is more favorable than others, as the electrical stimulation may be delivered to stimulate the peripheral portion of the retina preferentially. This is in contrast to optical stimulation which preferentially evokes cortical responses from the central or macular portion of the retina. In order for the visual evoked response to be useful as the criterion for the positive detection of the effects of high G forces, the loss of visual function should occur as early as possible. Also, as the electrical responses stimulate mainly the peripheral retina, any changes in the perception of visual space due to a combination of the electrical stimulation with the optical signal in the most peripheral portion of the environment will be less noticeable and degrade visual function in the less important portions of the visual field.

SCIENTIFIC BACKGROUND OF THE PROGRAM

The scientific background can be considered under two headings: the current state of research on the use of visual evoked cortical potentials to monitor retinal function; and the scientific background for the electrical stimulation of the retina from external sources.

Current Status of Research on the Use of Visual Evoked Cortical Potentials to Monitor Retinal Function as an Indicator of "G" Tolerance.

The limitations of "G" tolerance by pilots can be far exceeded by modern high performance jet aircraft. The driving force of the heart is often not sufficient to force blood into the brain against the downward thrust of blood resulting from accelerations attendant upon aircraft maneuvers. As the blood pools in the legs and abdomen, the eyes and brain are not supplied with freshly oxygenated blood. This results in loss of visual sensitivity, first in the periphery, and then in the central areas. This can be followed by total blackout and unconsciousness, all in a rapid sequence.

The Naval Air Development Center has an extensive program on blackout detection, and much of the following background material is based on an extensive review of that program by Cohen (1979).

Normal intraocular pressures are between 8 and 20 mm Hg, usually about 12 mm Hg. This intraocular pressure means that the blood flow to the retina is impeded with respect to that through the cortex, to a certain extent. Because of this the retina becomes ischemic at about one G less downward acceleration than the brain itself. Thus, with downward G forces visual changes generally precede the loss of CNS functioning, and human tolerance to downward G forces has often been based on visual performance criteria.

In general, total anoxia affects the cortex first and progresses to the lateral geniculate nucleus, then to the retina, working its way peripherally to the photoreceptors (Brown & Watanabe, 1965). However, during downward acceleration, the effect of blood stagnation is first manifested in the inner layers of the retina where, as the local arterial pressure falls, the normal intraocular pressure occludes the blood vessels beginning with the capillaries. As the resistance to blood flow is higher in smaller vessels, and the caliber of the capillaries generally decreases towards the periphery, the peripheral vessels are more sensitive to blood changes than the more central ones, and function is lost first in these peripheral regions (Ward, 1968). This loss of peripheral vision, progressing to loss of central vision and blackout, is attributed to retinal ischemia. These retinal events have long been considered to be the precursors of unconsciousness due to cerebral hypoxia (Doolittle, 1924; Duane, 1954; Fraser, 1966; Leverett, Kirkland, Schermerhorn & Newsom, 1966; and Mercier and Duguet, 1947).

Visual blackout in unprotected and uncompensated human subjects in acceleration environments is probably not a simple process due only to mechanical consideration and blood flow (Betz, 1972; Krutz, Rositano, & Mancini, 1975). Nevertheless, a consideration of blood flow in the eye and brain is sufficient to show how some currently employed methods for enhancing human resistance to downward acceleration may act.

The simplest method to enhance resistance to downward acceleration is to place the subject with his back toward the acceleration. This replaces the head-to-toe accelerative forces by chest-to-spine forces. In this position the subject can tolerate more than 11 Gs. Enhanced resistance to blackout also results when the blood is prevented from pooling in the lower extremities and

the abdomen. This increases the circulating blood volume. Blood pooling can be prevented by inflation of the bladders in a conventional G-suit. This can provide between 1.5 and 2.0 Gs additional protection. Straining maneuvers in which the subject exhales against a closed or partially closed glottis (the L1 and M1 maneuvers) increase intrathoracic pressure, diminish blood pooling, and can provide up to two Gs protection.

In order to use these protective measures, it is necessary to obtain methods for evaluating G tolerance that have the following characteristics:

1. High reliability and reproducibility.
2. Physically and behaviorally non-invasive.
3. Provide objective end points.
4. Insensitivity to experimental artifacts.
5. Give rapid on-line, real time discrimination.
6. A useable margin between the determination of G tolerance and the boundary of unconsciousness.

Behavior measures of the visual system function lack stability and in a functional sense are usually quite invasive. Only objective measures of the integrity of the visual system during retinal ischemia seem able to meet these criteria.

The NADC program (Cohen, 1979) is based upon the work of Duane et al, 1962, who demonstrated visually discriminable photic driving of the filtered EEG which followed the frequency of this test light. Some subjects exposed to accelerative forces in the human centrifuge showed loss of peripheral light sensitivity and photic driving of the EEG, along with collapse of the retinal arterioles. Blackout occurred in the systolic phase collapse. Photic driving ceased before grayout or dimming of the pheripheral visual field.

Visual evoked responses (VER) may furnish another objective test. As summarized by Cohen (1979), improvements in electronics, along with real time digital computer processing methods, now allow the reliable detection of small amplitude bioelectrical signals. Since changes in visual function should provide a reliable indicator of G tolerance (Coburn, 1970; Gillingham & Krutz, 1974) and since both the visual evoked cortical responses (Donchin & Lindsley, 1969; Richards, 1977) and electroretinograms (Tepas, Armington & Kropfl, 1962; Ward, 1968) have been shown to provide reliable indicators of visual functioning, it appears these techniques may furnish a simple, yet reliable, approach to the determination of human tolerance to acceleration. To some extent recent work at NADC has borne this out (Nelson and Hrebien, 1982).

The electroretinogram (ERG) is generated by the retinal receptors (negative a-wave) and the neural activity of the inner layers of the retina (positive b-wave) according to Ward (1968). The appearance of the various components of the ERG gives a measure of retinal ischemia and thus, G tolerance. The ERG response to a high luminance stimulus is much easier to detect than the VER. However, the ERG almost disappears as stimulus luminance decreases, while the VER still remains quite detectable. In this way, the ERG may be a better indicator of retinal function than the VER. Ward (1968) has observed that the amplitude of the ERG b-wave was markedly diminished in anesthetized beagles exposed to downward acceleration, and disappeared completely when the acceleration was doubled. Also, the ERG is an area effect, and thus photometrically represents peripheral retinal responses. In this point, the ERG has an advantage over the VER. The value of the ERG for detection of detrimental G forces in humans is not presently known, however.

The ERG and the VER both depend upon potentially annoying visual stimulation. However, recent work at NADC (Nelson and Hrebien, 1982) shows that the VER may be much less dependent than the ERG responses. On the other hand, the VER preferentially represents the central retinal responses. Thus, it may be that an alternative electrical response which combines the minimal visual distraction of the VER with the high sensitivity to peripheral retinal integrity of the ERG, such as the electrical stimulated cortical response (EER), could be a suitable measure of visual system function in an acceleration field to be used operationally as an early warning of blackout. This program was designed to evaluate the possible development of the EER as an early warning for blackout during positive G.

Scientific Background for Electrical Stimulation of the Retina from External Sources.

The response of the visual system to electrical stimulation has been reviewed by K. Motokawa (1949) in a comprehensive fashion. Previous investigations have been devoted to the perceptual responses of electrical stimulation of the eye, and to the perceptual assessment of electrical stimuli presented in conjunction with flashes of light in various patterns within visual space. Most subjects perceive stimulation of the retina as equivalent to a diffusely presented light in the peripheral portion of the retina. The threshold of this electrical response in the retina is greatly lowered by the ambient illumination. Also, the electrical excitability of the retina varies with a fixed time course after illumination (Motokawa, 1949). This indicated that the frequency of electrical stimulation and its relation to the frequent content of illumination of the eye must be considered as interactive elements and will greatly modify the response.

The electrical excitability of the retina has been used as an indicator of oxygen deficiency (Motokawa & Iwama, 1949). In these experiments, the perceived response to electrical stimulation was measured as the inspired 0_2 partial pressure was changed. However, this data is ambiguous. The tests were conducted on dark-adapted subjects in order to get maximum sensitivity. Nevertheless, there was a difference between the threshold levels with ascending and descending 0_2 levels, as compared with a normally oxygenated subject. Only three thousand meters were achieved in the decompression chamber, with minimum oxygen saturation of the blood still well above that where additional oxygen is normally administered. The administration of oxygen to the whole body prevented the low ocular and cortical levels which are achieved during or just before blackout, which are the levels really needed for operational purposes. The responses to visual stimulation were very similar to those elicited by electrical stimulation, although electrical stimulation seemed to be more sensitive.

Flickering light has been used in conjunction with pulsating electrical stimulation. The quantified approach to interaction used indwelling electrodes to stimulate the retina. The cortical responses to this type of stimulation have been investigated in some detail by Dawson and Radtke (1977). They have an extensive bibliography of previous attempts to do the same thing. On the basis of this review and their own experimental data, they have concluded that the eye is comparatively refractory to electrical stimulation in the dark. However, when the retinal threshold dropped, the responses did not allow positive identification of the active region of the retina.

METHODS USED IN THIS PROJECT

Experimental Approach Used in the Present Program

We have examined the cortical responses to visual and electrical stimulation of the retina, and also the electroretinograms (ERGs) which accompany evoked cortical responses to visual stimuli and to electrical stimuli of the eye. All of these responses were recorded with normal intraocular pressure, and with elevated intraocular pressure. Some experiments were also made recording with intraocular electrodes from ganglion cells in the peripheral part and the central part of the retina in order to determine the differential sensitivity of these cells to increases in introcular pressure.

The overall objective of this program was to use scalp electrodes in the region of the inion to measure cortical potentials evoked by external electrical stimulation of the eye as a test for the occurrence of peripheral retinal ischemia.

The retinal ischemia was induced by compromising the retinal blood flow with increased intraocular pressure applied manometrically.

Animal Selection

Rhesus (or closely related types) monkeys are usually chosen for all animal experiments whose data will be correlated with previous (and future) behavioral experiments to be applied to human operational situations. However, rhesus monkeys are unsuitable for use in gathering pilot data because of the difficulty in maintaining them for long periods of time to collect data from pilot experiments or the expense of keeping them for long periods of time. However, previous work has shown great similarities between the cat retina (and visual system) and that of the rhesus monkey, even though the cat retina lacks a fovea. The cat retina does have an area centralis, with ganglion cell receptive fields which resemble very closely those in the area in the monkey (and human) retina immediately adjacent to the fovea. The low cost of cats makes it possible to do large numbers of pilot experiments. All of these factors made it advantageous to gather large amounts of data on the cat retina initially.

The animal was mounted in the optical stimulator with the eye immobilized by an ocular muscle clamp. A corneal contact lens was attached to correct refractive errors. An intraocular recording electrode was inserted through a small hole in the side of the eye, at the pars plana, to avoid detaching the retina, by a method which maintained the intraocular pressure at the desired level. A catheter was inserted through another location on the pars plana to allow direct manometric control of the intraocular pressure.

Anesthesia and Surgery

All experiments were carried out under either general inhalation anesthesia or I.V. administered pentabarbitol choloride anesthesia. All animals were initially anesthesized with ether. When a suitable depth of anesthesia was obtained either pentabarbitol was infused to keep the animal at a level sufficient to suppress any reflex responses to corneal stimulation or intratoe web pressure or a general inhalation anesthesia was used with a 70% nitrous oxide 30% oxygen mixture. An intravenous infusion of gallamine triethoxide (Flaxedil), 5-10 mg/cc of saline at the rate of 130 mg/kg body weight/hour. The animal was intubated and was respired artificially with a ventilator (Harvard Apparatus Company, Model 661). Inhalation anesthesia was maintained with a 70% nitrous oxide 30% oxygen mixture throughout the experiment. The expired pCO_2 was monitored continuously by a Beckman Model LB-1 Medical Gas Analyzer with the aid of an

indicator alarm (Electrodyne MS-25). The CO_2 level was kept at 4.7%. In addition to the control of gas mixture flow furnished by the anesthesia machine, (Ohio Chemical and Surgical Instrument Company, Model 212B), a manometer was installed to avoid any damage to the animal's lungs from over pressure during the inspiration and exhalation part of the respiratory cycle.

Animals are maintained at normal body temperature by means of a heating pad. These life-support systems are adequate to maintain a cat in satisfactory physiological condition for up to 48 hours, although the experimental sessions were never more than 8 hours long, in order to insure uncomplicated recovery from the anesthesia.

The infusion of gallamine triethoxide with dextrose and saline was continued throughout the reporting session to assist in fixing the eye. A local anesthestic, (5% lidocaine ointment) was applied to the surface of the conjunctiva before any incision was made, and to all other incision pressure points.

In all experiments, the animals are under deep ether anesthesia during all surgical procedures. The level of ether anesthesia was sufficient to terminate spontaneous respiration and the animal required artificial inhalation. In addition, all incisions were filtrated with a local anesthestic. Only after surgery ended was the ether discontinued. Either a 70% nitrous oxide 30% oxygen breathing mixture or a sodium pentabarbitol infusion was used for a continuing anesthesia. The insertion of electrode through the pars plana involved no pain. This procedure is similar to operations that are often performed on humans with only a local anesthestic. During the experiment the heart rate was continuously monitored, and at no time were heart rate changes detected which would be associated with pain perception.

Although nitrous oxide, even at high, partial pressures, does not produce surgical anesthesia (Brown et al, 1927; Venes et al, 1971), it has been established that a 70% nitrous oxide 30% oxygen mixture in oxygen produces a high degree of sedation and analgesia in both cats and monkeys. It is an adequate anesthestic when only mildly noxious stimulants are present; for example, the direct stimulation of peripheral nerves at frequencies up to 3 Hz., or foot pad shock, (Venes et al, 1971).

Gallamine triethoxide is not required to relax the animal, but assisted in maintaining the high degree of immobility required to assure that both the electrical and visual stimulations were the same at all times during the experiment. It has been established that gallamine triethoxide has no effect on the retinal ganglion cell responses of cats and monkeys (Enroth-Cugell and Pinto, 1970). Because of these considerations, nitrous oxide and gallamine triethoxide have routinely been used for experiments of this type. Nitrous oxide has been used by us and others because it has only slight side effects in evoked visual responses as compared to strong central depression produced by other volatile anesthestics and barbituates (Van Norren and Padmos, 1977). The depressive action in the retina has also been seen with some of these other anesthestics as well (Van Norren and Padmos, 1977). Obviously it is important to minimize CNS effects from the anesthestic when studying the activity of the visual system, especially when using the evoked cortical responses.

The iris was dilated and accommodation relaxed with several doses of Duke mix (10% phenylephrine; 0.5% mydriacyl, 1:1) applied every hour.

Optical Stimulation

The basic optical stimulator has been described in detail in previous reports and other publications; Wolbarsht and Ringo, 1980; Crocker et al, 1980, and Wagner et al, 1960. It has two channels with essentially equivalent pathways. Since the special features of this optical system are not relevant to the present experiment, it is not necessary to describe the equipment in detail. This equipment is capable of delivering reproducible light pulses to selected retinal areas. The spatial extent, duration, and wavelength of the stimulus can all be controlled independently. A Grass photoflash stimulator (Model PS-22A) was also used to give a visual stimulus which could be correlated with previous work on the visually evoked potentials as recorded in the cortex.

Electrophysiological Recording Apparatus

The electrical stimulus was delivered to the eye through paired cheek and brow electrodes, or paired electrodes mounted at the inter and outer canthus of the eye. Occasionally a standard corneal contact lens was used for stimulation in order to minimize the stimulus artifact, the electrical stimulus was generated by a (Tektronix Type 161 Wave Form Generator and a Tektronix Type 162 Pulse Generator), with a power amplifier constructed locally from a design furnished by E. F. MacNichol, Jr. A circuit diagram of this power amplifier, is shown in Figure 1. The power amplifier was connected to the animal through a Grass Stimulus Isolation Unit (SI-1) in order to minimize artifacts in the recording system, which would interfere with the detection of the cortical responses. All physiological electrical responses were recorded by FET input stage amplifier of conventional design.

In preliminary experiments an incision through the skin along the midline of the head was made to remove the underlying tissue. Tungsten wire recording electrodes were implanted in the skull along the midline, 60 and 80 percent of the distance from the inion and the nasion. Also conventional EKG electrodes were used on the shaved but intact scalp above the inion and at the points overlying those for the implanted electrode locations described above. Two types of stimulus electrodes were used, a corneal electrode built into a plastic contact lens (Grass E-2 Platinum Needle Electrode), and a stainless steel electrode placed on the mucus membrane near the corner of the eye. In some cases EKG electrodes were used on the shaved brow and lower lid. In both of these cases an ipsilateral cheek electrode was used.

The responses were processed with a Nicholet Signal averager with the following time constants unless noted on the figures: 12 X 640 ms, 0 delay, filter 0.02. All leads were capacity coupled.

The visual evoked potentials (VER) were obtained by stimulating the eye with either 300 ms or 10 ms pulses of light at a repetition rate of 1 per second through the 2 channel Maxwellian view optical system.

The intraocular pressure changes were obtained by lengthening or shortening the height of a column of saline connected to the vitreous cavity through a needle piercing the cornea or the pars plana.

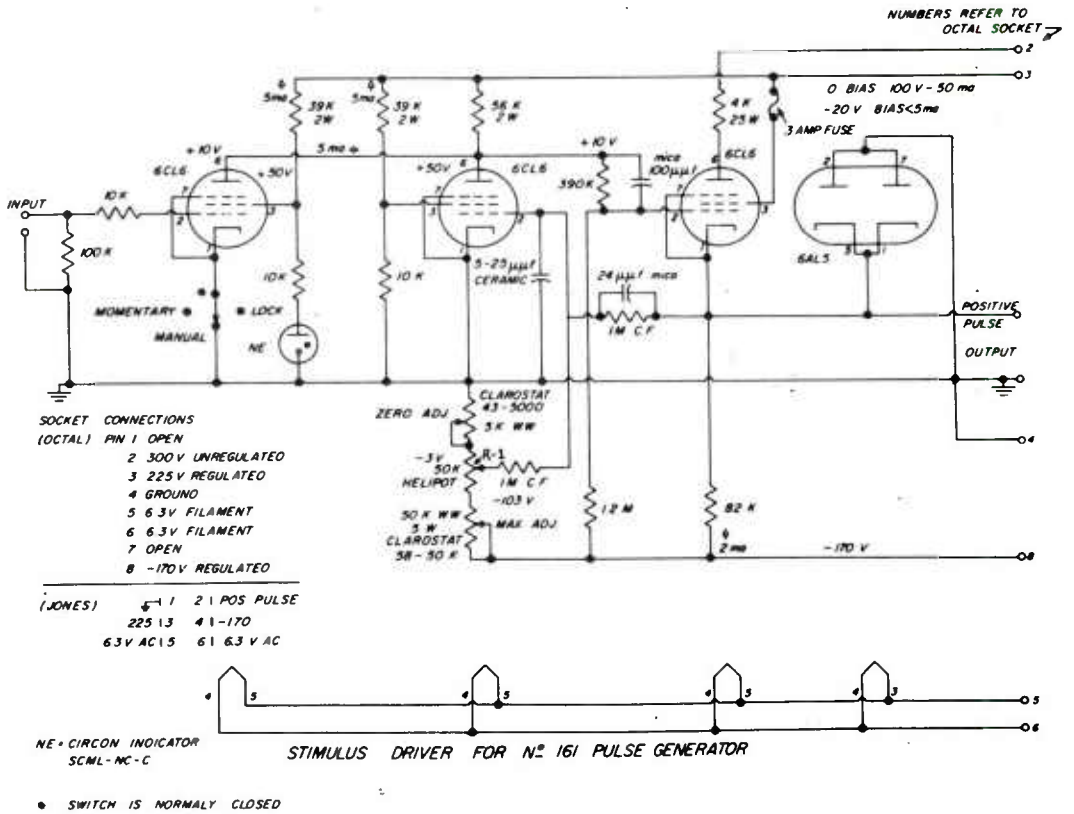

Figure 1. Stimulus Power Amplifier. This circuit is based on a design by E. F. MacNichol, Jr., and is constructed on a chassis compatible with the Tektronix series pulse and wave form generators, and uses the type 160 power supply. The amplifier emits a pulse of 0 to 100 volts (controlled by resistor R1) whose duration is the same as the negative pulse delivered to input. This stimulus driver was designed to be used in conjunction with the Tektronix #161 Pulse Generator. It is capable of delivering a square wave pulse continuously variable in amplitude between 3 v to 100v. The wave form has a rise and decay time of 2.5 sec when working into a 5k lead. This square wave form is preserved at 100v amplitude through 2.3k load before 5% fall off is noticed. Below this load the output deteriorates rapidly. If there is no signal applied to the input of the first 6CL6, sufficient plate current flows to cause the output 6CL6 to be in the cut-off condition; thus the OUTPUT is clamped by 6AL5 at approximately ground potential. A negative potential of about 10v applied to the INPUT (junction 100k and 10k) 6CL6 causes the plate current to decrease and thus the bias on output 6CL6 to be less, allowing the cathode potential of 6CL6 (output) to be positive of ground giving a sharp front pulse out. The feedback from the cathode of output 6CL6 to the grid of middle 6CL6 determines the top of the output pulse. The d.c. potential on this grid will be one half the difference between the potential of the output cathode and the potential on the slider of R-1. Since this is a precision output calibrated potentiometer the height of the pulse can be read directly in volts. The zero adjust pot should be placed approximatley in the middle of its range or until the bottom of the wave form is approximately a straight line (about -3v). The position of maximum adjust pot will determine the maximum pulse height. This should be 100v above the zero base line (-103 to -106v on the bottom of Helipot). The pulse shape may be corrected to give a square front by the capacitor on the grid of the middle 6CL6. In the event the output is to be used in conjunction with an isolation transformer, more satisfactory results will be realized if a 6AL5 limiting diode is used. The power to operate the unit is taken from the Tektronix #160 power supply and fed through a male octal connector located on the back of the unit. The 6 pin Jones connections will drive the Grass stimulus isolation unit, SI-1.

RESULTS

Electrical Evoked Responses From Corneal Stimulus Electrodes.

EERs were recorded using a stimulus electrode implanted into plastic corneal contact lens. This gave an easily detected cortical response. The maximum ERR was obtained in the stimulus voltage of about 0.550 V at a duration of 10 ms. The normal intraocular pressure in a cat is from 12 to 18 mm mercury 16 to 24 cm water. When the intraocular pressure was raised to 118 mm Hg 155 cm of water, both the visual evoked response and the electrical evoked response were eliminated. When the intraocular pressure was lowered to a more normal level, 18 mm Hg or below, both the visual evoked potential and the electrical evoked response returned. This raising of the intraocular pressure and lowering of it with complete return of the response could be repeated several times during a single recording session. The pressure cycling seemed to have no adverse effect on the eye as long as the elevated pressure phase was not maintained for more than five minutes.

The best responses were obtained with the stimulus artifact negative with respect to the response. Since the stimulus was electrically decoupled from the cat as much as possible, the stimulus artifact in the recording was low. Both polarities of the stimulus pulse had to be tried in order to obtain the maximum signal-to-noise ratio for the response. Since the electrical evoked response was eliminated by high intraocular pressure and reappears when the pressure is lowered, this implies if the electrical stimulus is indeed acting at or before the ganglion cell layer.

Electrical Evoked Responses from Stimulus Electrodes at the Inner and Outer Canthus.

The EER recorded with a stainless steel electrode placed on the mucus membrane at the inner and outer cathi had a higher threshold than that for corneal contact lens, 1.25 volts versus 0.950 volts for the corneal electrode. However, canthal electrodes appeared to be better for stimulating the more peripheral portions of the retina. This was measured by the disappearance of EER from this stimulus at a lower intraocular pressure than that required to abolish completely the response from the corneal contact lens stimulating electrode.

The responses for cheek and brow electrodes are more difficult to obtain consistently. However, results with EKG electrodes with well-moistened electrode paste and some kind of moisture shield (Saran Wrap) over the electrodes to eliminate evaporation gave the best and most consistent results. However, such an electrode moisture shielding system might be difficult to arrange in an operational situation.

Recordings of the local electroretinogram (ERG) with tungsten electrodes inserted through the pars plana were helpful in determining which portions of the retina ceased function earliest with increases in intraocular pressure. The tungsten electrode was advanced visually through the opening on the pars plana until the tip just approached the retina, within 50 or 100 micrometers. In this manner, peripheral retinal locations lost their b-wave and later components at lower intraocular pressures than more centrally located recording sites. Initial attempts to use the intraocular electrodes as stimulus electrodes to stimulate preferentially different parts of the retina in order to determine the particular type of electrical evoked cortical response characteristic of different types of retinal stimulation were largely unsuccessful due to persistent and large electrical stimulus artifacts in this recording condition. This artifact eliminated most of the time domain in the response available for the conventional evoked response. However, some more work will certainly eliminate this problem.

The initial experiments in this study were directed towards the development of techniques for the most efficient and consistent recording of cortical responses to visual stimuli.

Once suitable electrodes were found and the optimal electrode locations established for the recording of the visually evoked response (VER), we proceeded to initiate electrical stimulation in a series of cats, using the VER as a control to ensure that the recording system was functioning.

Since the electrically evoked response (EER) is presumably initiated by the ganglion cells and conducted through similar pathways in the brain as the VER, we also used the VER as a control to establish the cessation of ganglion cell function upon raising the IOP. Finding an elimination of the EER under such conditions indicates that the EER is, indeed, a retinal phenomenon, rather than a direct optic nerve stimulation or artifact of some other sort.

Both systems of stimulation for EER with both electrodes in the antero-temporal dermis, or with a dermal reference electrode with a corneal contact lens stimulating electrode give similar responses. Responses from electrodes in the inner and outer canthi were readily obtainable and surprisingly similar in different cats. To all stimuli we also observed a clear "on" response and "off" response, which would "migrate" on the trace according to duration of the stimulus. The VER was consistently suppressed by raising the IOP to 155 cm H_2O, with return after the IOP was returned to normal. The optimal stimulus was in the neighborhood of 1 V, with a duration of about 10 msec. This was a true EER, since it was suppressed along with the VER when the IOP was raised. Also, it returned after the IOP was reduced to normal. Interestingly, a similar EER was elicited through either polarity of stimulus, the only difference being an inversion of the stimulus artifact. It was noted in one experiment that injection of lidocaine and pentabarbitol into the anterior chamber had little or no effect on the VER.

Our data show that the function of the peripheral retina can be detected by electrophysiological techniques. The experimental work during the present program was directed towards the verification that cortical responses seen following electrical stimulation of eye were verifiably from the peripheral retina rather than artifacts. Recording from retinal ganglion cells whose receptive fields are in the peripheral portions of the retina, and recordings from the visual cortex as seen by scalp electrodes over the inion both show clearly and reproducibly identifiable responses to electrical stimulation. The stimulating electrodes can be placed on the upper and lower lids (cheek and brow) or on the inner and outer canthi. Both responses are abolished when the intraocular pressure is raised. Figure 2 shows a normal electrical evoked response (EER) and in Figure 3 for comparison has a normal visual evoked response from the same eye. Figures 4 and 5 show responses from the same stimuli after raising the intraocular pressure.

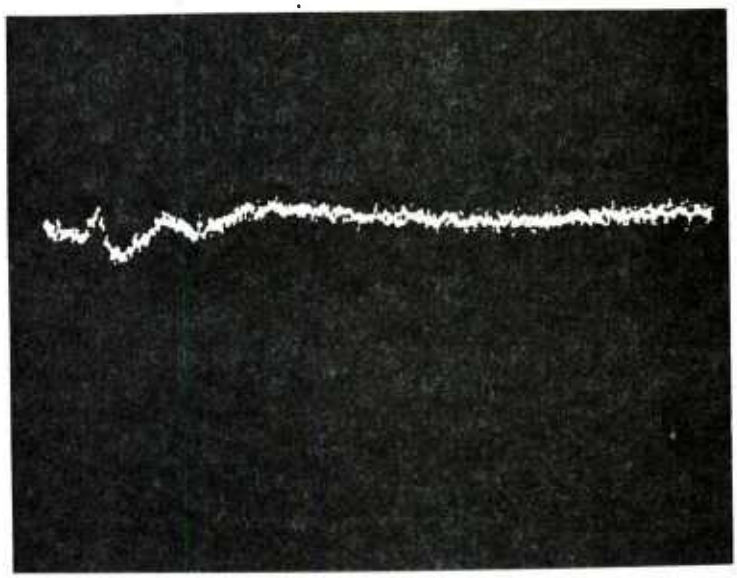

Figure 2. Evoked cortical response to visual stimulation of the cat eye (VER). The multipeak response is normal, and highly reproducible. The intraocular pressure 15 mm Hg and the recording electrodes are on the skull midline anterior to inion.

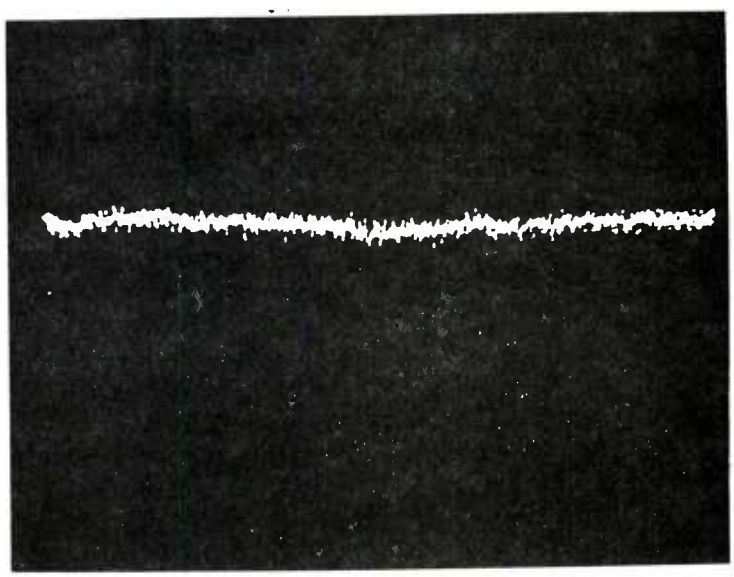

Figure 3. Evoked cortical response to visual stimulation of the cat eye (VER). Intraocular pressure 150 mm Hg. The recording electrode location, stimulus, pulse, duration and intensity and parameter are the same as in Figure 2. The reponse returns to the level in Figure 2 when the pressure is returned to 15 mm Hg.

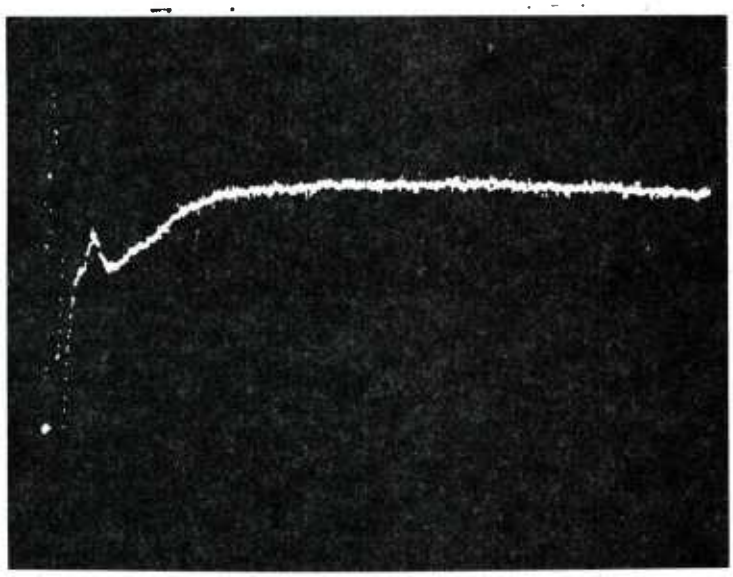

Figure 4. Evoked cortical response to electrical stimulation of the cat eye (EER) at norm intraocular pressure. Intraocular pressure 15 mm Hg. Inner and outer canthus electrodes. 0.8 V, 2 ms stimulus pulse. Recording electrodes on the skull midline anterior to inion. The multipeak response is normal and highly reproducible.

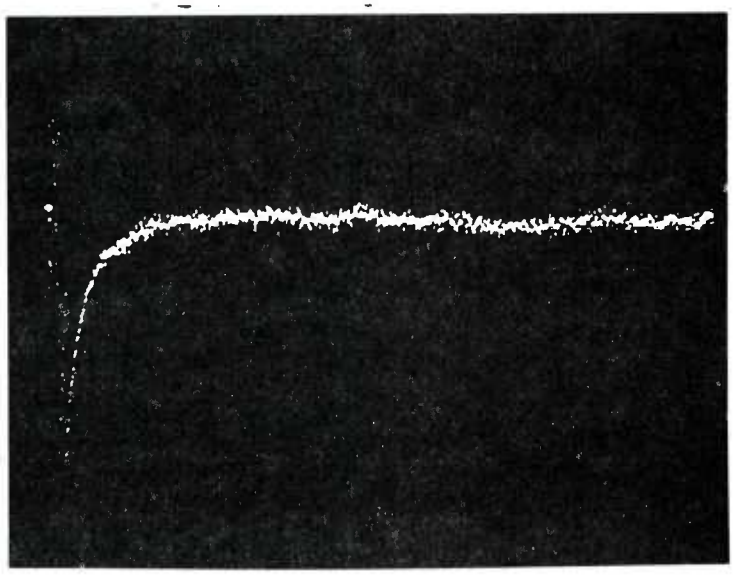

Figure 5. Evoked cortical response to electrical stimulation of the cat eye (EER) at elevated intraocular pressure. Stimulus and recording conditions as in Figure 4. This response is recorded ten minutes after intraocular pressure has been raised to 120 mm Hg. All traces of the EER have disappeared. Elements of the neural response appeared within one minute after the intraocular pressure was returned to normal, as shown in Figure 4.

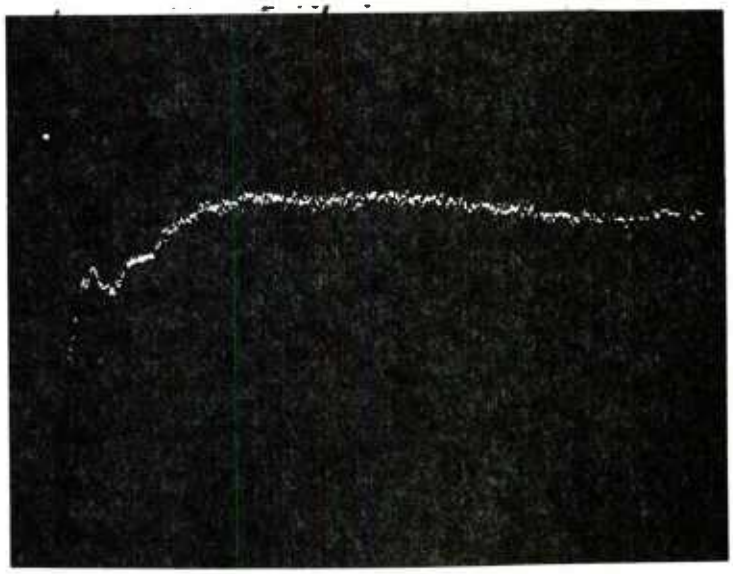

Figure 6. Evoked cortical response to electrical stimulation of the cat eye (EER) after increased intraocular pressure. This response was recorded one minute after the intraocular pressure has been returned to normal (15 mm Hg) after remaining ten minutes at a pressure of 120 mm Hg. Stimulus and recording conditions as in Figure 4.

CONCLUSIONS

No quantitative data has been gathered yet on the EER, and several important questions remain unanswered. For example, is the response gradually abolished as the intraocular pressure is raised, or as the peripheral circulation is compromised? And, also, it may be that both the VER and EER are abolished, not by oxygen lack or build-up of some metabolite due to stagnant or absent blood in the peripheral retina, but rather to deformation of the optic nerve at the disc while the intraocular pressure is raised. Our future research plans call for causing the carotid circulation on one side to be cut off so as to compromise the retinal blood supply without at the same time changing the nerve configuration at the disk due to changes in intraocular pressure. More retinal recordings in the center and periphery will aid in determining if those responses are abolished sequentially by the raised intraocular pressure.

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